Remarks

Claims 2-3, 6-28, and 30-42 are pending. Claims 2, 17, 19, 21, 23, 25, 32, 34, and 36 have been amended. Claim 37 has been canceled.

Rejection Under 35 U.S.C. § 112, first paragraph

A. Claims 2-3, 6-28, and 30-42 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. The Office Action bases this rejection on the alleged failure of the specification to disclose a representative number of species and on the alleged definition of the claimed nucleic acid sequences only by a statement of function. However, as neither of these premises are correct, Applicants respectfully traverse this rejection.

The courts have clearly established that the first paragraph of 35 U.S.C. § 112 includes, *inter alia*, two separate requirements: (1) an enablement requirement based on the statutory language that the application describe "the manner and process of making and using [the invention], in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same," and (2) a written description requirement based on the statutory language "[t]he specification shall contain a written description of the invention" (the third requirement of the first paragraph of 35 U.S.C. § 112, the "best mode" requirement, is not relevant here). The separate status of the make and use clause and the written description clause was at the heart of the recognition of the separate written description requirement. *See* Vas-Cath v. Mahurkar, 935 F.2d 1555, 1560-61 (Fed. Cir. 1991); Enzo Biochem v. Gen-Probe, 285 F.3d 1013, 1018, 1021 (Fed. Cir. 2002) (hereafter "*Enzo I*")).

The essential goal of this written description requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed. *See In re Barker*, 559 F.2d 588, 592 n.4, 194 USPQ 470, 473 n.4 (CCPA 1977). Another objective is to put the public in possession of what the applicant claims as the invention. *See The Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1566; 43 USPQ2d 1398, 1404 (Fed.

Cir. 1997) (hereafter, "*Lilly*"). *Lilly* established *inter alia* that, in the case of claims to genes, an adequate written description requires more than the name of the gene and a statement of its function, it "requires a precise definition, such as by structure, formula, chemical name, or physical properties." *Lilly*, 119 F.3d at 1566; 43 USPQ2d at 1404.

The Patent Office undertook a review of the written description caselaw in view of *Lilly* in order to establish guidelines for the examination of patent applications for compliance with the written description requirement of 35 U.S.C. § 112, first paragraph. *See Guidelines for Examination of Patent Applications Under 35 U.S.C. 112, ¶1 "Written Description" Requirement*, 66 Fed. Reg. 1,099 (Jan. 5, 2001) (hereafter, "*Written Description Guidelines*"). Far from requiring any absolute or *per se* requirement for adequate written description, the resulting *Written Description Guidelines* provide a case-specific and fact-dependant inquiry. This is consistent with caselaw, where compliance with the written description requirement is consistently referred to as a fact-dependent inquiry. *See, e.g., Vas-Cath v. Mahurkar*, 935 F.2d 1555 (Fed. Cir. 1991).

Importantly, compliance with Written Description is based on the ability to distinguish the claimed composition or method from others. The *Written Description Guidelines* note that "[a]ctual reduction to practice may be crucial in the relatively rare instances where the level of knowledge and level of skill are such that those of skill in the art cannot describe a composition structurally … in such a way as to distinguish the composition with particularity from all others." *Written Description Guidelines,* Response to Comment 7, pg. 1101. Thus, there is sufficient Written Description if the metes and bounds of the claimed genus are clear such that the skilled artisan can determine if a given compound is covered by the claim.

Moreover, the USPTO has already established that a genus of sequences can be claimed based on sequence identity to a specific sequence (see Example 14 of the U.S.P.T.O. "*Synopsis of Application of Written Description Guidelines*")(hereinafter "*Synopsis*"), wherein it is stated:

> [t]he single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants…which are capable of the specified catalytic activity.

(*Synopsis*, page 54, fourth paragraph). Thus, the *Guidelines* and *Synopsis* specifically sanction the use of percent identity claims of reasonable scope. However, examiners do not appear to be following this direction.

In contrast, the Board of Patent Appeals and Interferences (BPAI) has been very consistent when it comes to written description rejections of percent identity claims. A recent review of decisions by the BPAI revealed six cases where the Board reversed an examiner's written description rejection of a percent identity claim, and not a single instance where such a rejection was affirmed.[1]

Most notably, in *Ex parte Sun,*[2] the examiner pointed out that the patent specification failed to disclose a single example of a wee1 variant retaining the activity of wee1 and sharing only 80% identity with the reference sequence, and "argued that the 'specification does not set forth what specific structural or physical features define the claimed isolated nucleic acids,'" and "that one skilled in the art could not predict the structure and function of isolated nucleic acids comprising a wee1 polynucleotide having at least 80% identity to the entire coding region of SEQ ID NO:1.'" *Id.* at 7-8. The Board noted however that "predictability is not the legal standard or test for [written description] rejections" and dismissed the examiner's argument that the specification failed to teach a single representative species within the genus. The Board therefore reversed the written description rejection, citing *Enzo II* and holding that the disclosure of the single reference sequence and methodology for screening for variants having Wee1 activity was sufficient to satisfy the written description requirement. *Id.* at 8-9, 11. *See also Ex parte Bandman,*[3] *Ex parte Au-Young,*[4] *Ex parte Meyers,*[5] *Ex parte Bandman,*[6] and *Ex parte Smith.*[7] Note that these Board decisions are being cited for informational purposes only as they are not intended as binding authority.

---

[1] Christopher M. Holman, *Is Lilly Written Description A Paper Tiger?: A Comprehensive Assessment Of The Impact Of Eli Lilly And Its Progeny In The Courts And Pto*, 17 Alb. L.J. Sci. & Tech. 1, 44-47 (2007).
[2] Appeal No. 2003-1993, Application No. 09/470,526 (B.P.A.I.)(not written for publication)
[3] Appeal No. 2003-1805, Application No. 09/079,892 (B.P.A.I.)(not written for publication)
[4] Appeal No. 2003-1817, Application No. 09/501,714 (B.P.A.I.)(not written for publication)
[5] Appeal No. 2003-1820, Application No. 09/464,039 (B.P.A.I.)(not written for publication)
[6] Appeal No. 2004-2319, Application No. 09/915,694 (B.P.A.I.)(not written for publication)
[7] Appeal No. 2005-0147, Application No. 10/203,081 (B.P.A.I.)(not written for publication)

Here, the pending claims define the genus of nucleic acids entirely by sequence identity to a reference sequence (i.e., by structure). By writing out the sequence of a reference molecule (e.g., SEQ ID NO:4) and by defining a genus of molecules by percent similarity to the written out sequence, the specification has disclosed the sequence of every molecule that falls with in the percent similarity limitation. The fact that not every molecule in the structurally defined genus is literally written out in the specification, does not alter the reality that they are all disclosed. Therefore, the Office Action is incorrect in asserting that "it is not possible to envision the claimed composition" due to a failure "to disclose a representative number of species." This is because every single species of the genus is strictly identified based on sequence identity to the reference sequence. These species defined by sequence identity to a disclosed sequence are, thus, disclosed by their complete structure. This is not a situation where only a representative number of species has been identified by structure; rather all of the species in the recited genus are identified by structure in the specification and claims. Thus, the metes and bounds of the claims are clearly delineated such that the skilled artisan could literally envision every single member of the claimed genus. On this basis alone, the present written description rejection is improper and should be withdrawn.

Furthermore, the authorities cited by the Office Action to support this rejection are not applicable to the instant claims. For example, Applicants in *Fiddes v. Baird* claimed a DNA sequence encoding mammalian FGF but only taught a DNA sequences for bovine pituitary FGF. 30 U.S.P.Q.2d at 1481. Thus, neither the applicant nor the skilled artisan could predict what sequences would fall within the scope of the genus claim since a representative number of species were not provided to set the metes and bounds of the genus. In contrast, the present application discloses, by reference to the written out sequence, all of the sequences of the components of the claimed vector system.

Likewise, the Applicants in *Lilly* were attempting to claim human cDNA for human proinsulin while only providing the sequence for the rat cDNA. 119 F.3d at 1566; 43 USPQ2d at 1404. As the sequence of human proinsulin was not known at the time that application was filed, the skilled artisan could not know what was actually being claimed. In contrast, the present

application discloses, by reference to the written out sequence, all of the sequences of the components of the claimed vector system.

Moreover, the Office Action is incorrect in asserting that Applicants are attempting to claim sequences identified by a statement of function. This assertion would only be valid if the claim were to a composition comprising a nucleic acid encoding any protein that has the disclosed function, i.e., with no structural limitation. Such a claim would be attempting to describe the composition entirely by function and/or by a means of identifying compositions having that function. For example, that was the case in *Lilly*, where applicants were trying to claim a protein based entirely on a method of identifying the protein. In that case, there was no way to know if the protein existed, and if so, how similar the sequence would be to the protein found in another species. *Lilly* also stands for the position that one can only claim a genus of all mammalian proteins related to a novel protein identified in, for example, mouse, if a representative number of sequences are provided to indicate to the skilled artisan the amount of divergence across species and the subsequently conserved domains such that the artisan could reasonably determine whether a later identified protein fell within the scope of the claim.

In contrast, the present claims are limited by structure, e.g., to nucleic acids encoding an AAV4 capsid protein having at least 90% homology to the amino acid sequence set forth in SEQ ID NO:4. Applicants are not attempting to describe the genus based on a function or a method of identifying the compositions. Rather, every single member of the genus is strictly set forth by the sequence identity limitation. As shown above in the *Synopsis*, the fact that a functional limitation is provided such that the skilled artisan can test a construct within the genus to verify function is not equivalent to defining the construct by function. Instead, the construct is clearly defined based on its structure and a function is provided in the specification to allow the artisan to verify its utility. The fact that the claim also include reference to a utility/function, does not alter the fact that the molecules included in the claim are defined by structure as disclosed in the specification.

Thus, as the bases for the present rejection do not apply to the current genus claim, Applicants respectfully request the withdrawal of this rejection.

B. Claims 2-3, 6-28, and 30-42 were also rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled. The Office action appears to base this rejection on the above assertion that a reasonable number of species are not provided. Specifically, the Office Action asserts it would be undue experimentation for the skilled artisan to identify and characterize any and all of the variants of the AAV4 proteins that are capable of producing AAV particles. Applicants respectfully traverse this rejection.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification, coupled with information known in the art, without undue experimentation. *See United States v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988); *In re Stephens,* 529 F.2d 1343, 199 USPQ 659 (CCPA 1976)(determining enablement is a question of law based on underlying factual findings); *In re Vaeck,* 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991); *Atlas Powder Co. v. E.I. duPont de Nemours & Co.*, 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984).

Thus, a proper rejection on enablement grounds depends only on the question of whether, in view of the specification and the knowledge of those of skill in the art at the time the invention was made (as evidenced by the complete record in this application plus the body of knowledge available in the art at the time of filing), the compositions of claims 2-3, 6-28, and 30-42 could be made and used (for any specific and substantial purpose) by those of skill in the art without the need for undue experimentation.

One determines undue experimentation not by analyzing a single factor, but rather by analyzing and weighing many factors. The legal standard set out in *In re Forman* 230 U.S.P.Q. 564, 547 (Bd. Pat. App. & Int. 1986) and elucidated in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400 (Fed. Cir. 1988) sets forth the following factors for consideration: (1) the quantity of experimentation necessary (time and expense); (2) the amount of direction or guidance presented; (3) the presence or absence of working examples of the invention; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. It is not necessary that every enablement analysis consider all of the factors. *Amgen, inc. v. Chugai Pharmaceutical Co., LTD.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991).

The method claims at issue in *Wands* involved the use of an antibody wherein the "antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for . . . [the antigen] of at least 10^9M^{-1}." *In re Wands*, 858 F.2d at 734. This claim covers *any* monoclonal antibody, not just a specific monoclonal antibody, and the PTO argued that the Applicant failed to enable *all* monoclonal antibodies. *Id.* Briefly, the skilled artisan generates monoclonal antibodies by injecting an antigen into a host animal causing an immune reaction, isolating spleen cells, some of which produce the antibodies that bind the antigen, fusing the spleen cells with a cancerous myeloma cell producing a hybridoma, and then screening individual hybridomas to isolate those that produce antibodies that bind the antigen. *Id.* at 733-734. The PTO supported its non-enablement position by pointing out that 1) not all hybridomas produce antibodies that bind antigen, 2) not all hybridomas that bind antigen will bind with an affinity of 10^9M^{-1}, and 3) the applicants own data indicated that a small percentage of hybridomas actually produced monoclonal antibodies which fell within the scope of the claims. *Id.* at 738-739. The court rejected these arguments by stating,

> cell fusion [hybridoma technology] is a technique that is well known to those of skill in the monoclonal antibody art, . . .[t]here was a high level of skill in the art at the time when the application was filed, and all the methods needed to practice the invention were well known . . . [and] it seems unlikely that undue experimentation would be defined in terms of the number of hybridomas that were never screened, . . .[and since] Wands carried out his entire procedure three times, and was successful each time in making at least one antibody that satisfied all of the claim limitations . . . Wands evidence thus effectively rebuts the examiner's challenge to the enablement of their disclosure.
> *Id.* at 740.

Furthermore, the *Wands* court made clear that the amount of and type of experimentation considered undue fluctuates for each type of art. *Id.* The quantity of experimentation lacks relevance outside an assessment of what is "routine experimentation" in the art. *Id.* Thus, the huge amount of "experimentation" that the skilled artisan would have to perform to practice Wands' invention: immunizing an animal, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the hybridomas for the desired characteristics, *knowing that many hybridomas would not produce functional antibodies and* ***not*** *knowing which hybridomas would produced claimed antibody*, was not undue

experimentation because it was routine experimentation in the art of monoclonal antibody production. *Id.* As discussed below, the present claims and corresponding enablement rejection closely parallel the situation presented in *Wands* since the art of producing the presently claimed nucleic acid compositions encoding the genus of AAV4 peptides is routine experimentation in the art of recombinant nucleic acid and peptide design, even though it may seem complex. Furthermore, the fact that experimentation may be complex does not necessarily make it undue if the art typically engages in such experimentation. *See M.I.T. v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985).

Prior to applying the present facts to the relevant law, Applicants are compelled to point out that the Examiner has misrepresented a crucial fact of the present application. Contrary to the assertions of the Examiner, the previously amended and currently pending claims do not read on a vector system that comprises "any and all functional equivalent variants of Rep and Capsid proteins" (e.g., page 4, second full paragraph of the office action) or "any variant of AAV4 Capsid...or Rep..." (e.g., page 6, first full paragraph of the office action Because the description of the genus in the claims necessarily discloses the sequence/structure of every molecule included in the genus, describing this as reading on "any variant" of AAV4 Capsid/Rep is misleading at best. Recognition by the Examiner of the real scope of the claims seems to be necessary for a proper examination of the claims. Since it is not clear that the Examiner has made this recognition, clarification on this point is respectfully requested..

In the present case, the claimed vector system construct covers a genus of nucleic acids encoding an AAV4 capsid protein having at least 90% homology to an amino acid sequence set forth in SEQ ID NO:4. As in *Wands*, it is arguably possible that some constructs within the genus of nucleic acids will not have the desired ability to form AAV particles, and it is this possibility on which the present rejection is based. However, a *prima facie* case of obviousness is not established based solely on the potential need for experimentation in order to determine if a composition of the genus has the desired functional characteristics. As discussed in *Wands*, there are several factors to consider in determining whether the experimentation is undue, including (1) the quantity of experimentation necessary (time and expense); (2) the amount of direction or guidance presented; (3) the presence or absence of working examples of the invention; (4) the

nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. As discussed below, the function of the genus of proteins is highly predictable based on the level of sequence identity to the disclosed proteins. As such, the specification provides adequate guidance for the skilled artisan to test constructs within the genus to determine if they have the desired enzymatic properties.

For example, the knowledge and skill available based on prior studies of AAV2 vectors was such that the skilled artisan would be able to assay candidate AAV4 vector systems for the ability to produce AAV particles using routine experimentation. This screening process would be considered routine based on the quantity of experimentation necessary, the amount of direction or guidance presented, the presence of working examples, the nature of the invention, the state of the prior art, and the relative skill of those in the art.

Moreover, the function of sequences at least 90% identical to a known protein with a described function is highly predictable. It is generally understood that a molecule with 70% or greater homology to a known sequence will have the essential physical properties of the identified structure (see Tian, W. and Skolnick, J. J Mol Biol. 2003 Oct 31;333(4):863-82, attached herewith). Specifically, Tian and Skolnick evaluated the predictability of the enzyme commission (EC) number for proteins based on sequence identity. The EC number is numerical classification scheme for enzymes based on the chemical reactions they catalyze. The EC code consists of four numbers separated by periods. Those numbers represent a progressively finer classification of the enzyme, such that the fourth number generally represents the substrate specificity. Strictly speaking, EC numbers do not specify enzymes, but enzyme-catalyzed reactions. If different enzymes catalyze the same reaction, then they receive the same EC number. The findings of Tian and Skolnick indicate that most (~90%) enzyme mutants will maintain enzyme function with sequence identities as low as 60% and in fact enzyme function does not generally *start* to diverge until the sequence identity is below 70% (See Tian and Skolnick, abstract, page 863). The lowest percent identity claimed by the Applicant is 90%, and there is no evidence, either in Tian and Skolnick or in the art, that any mutations within this

range, other than those artisans would naturally avoid (e.g., stop codons), would in fact result in a non-functional mutant.

Thus, Applicants would expect with a very high level of certainty that any given sequence would function, and the skilled artisan would likely never pick a sequence that would not function. Further, while the skilled artisan has a high expectation that any given sequence having 90% identity would function, if needed, it is routine experimentation for one skilled in the art to test such variants to determine if they fit into the claimed homology and to assay said variant for functionality (e.g., AAV particle formation). Thus, as in Wands where the screening for IgM antibodies with a threshold binding affinity constant was determined not to require undue experimentation since the level of skill was high and the methods were well known, the assaying of candidate vector systems for the ability to produce AAV particles, also requires no more than routine experimentation since there is a high level of predictability that a given peptide within the defined genus will function.

Applicants therefore respectfully request the withdrawal of this rejection and allowance of claims 2-3, 6-28, and 30-42.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 2-3, 6-28, and 30-42 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Office Action posits that claims 2, 17, 19, 21, 23, 25, 32, 3[4] and 36 are allegedly indefinite for use of the claim limitation "about" to describe percent homology. In response, claims 2, 17, 19, 21, 23, 25, 32, 34 and 36 have been amended to recite "at least" instead of "about." Support for this amendment can be found on page 14, lines 17-20; page 18, lines 17-21; page 22, lines 17-22; page 23, lines 7-17 of the specification. Thus, no new matter is added by this amendment. The term "at least" is not indefinite in that it specifically identifies the metes and bounds of the claimed sequences. Thus, Applicants respectfully request the withdrawal of this rejection.

The Office Action further notes that claims 32 and 37 depend from canceled claims. In response, claim 32 has been amended to depend from claim 2 and claim 37 has been canceled.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

It is believed that no fee is due with this submission. However, the Commissioner is hereby authorized to charge any fees which may be required to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.

P. Brian Giles, Ph.D.
Registration No. 57,896

NEEDLE & ROSENBERG, P.C.
Customer Number 36339
(678) 420-9300
(678) 420-9301 (fax)

CERTIFICATE OF ELECTRONIC TRANSMISSION UNDER 37 C.F.R. § 1.8			
I hereby certify that this correspondence, including any items indicated as attached or included, is being transmitted via electronic transmission via EFS-Web on the date indicated below.			
Name of Person Mailing (Print/Type)	P. Brian Giles, Ph.D.		
Signature		Date	12-18-2007